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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,518	06/20/2003	Choong-Chin Liew	4231/2055	8219

29933 7590 08/11/2006

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,518	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,13,16,17 and 19-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13,16,17 and 19-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/05; 11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group II in the reply filed on 5/19/06 is acknowledged. The traversal is on the ground(s) that it would not be an undue search burden to examine the claims of both groups in a single application. Upon further reconsideration, the examiner has decided to rejoin the methods of group I and group II. Applicant's election, however, was not complete, as applicant did not elect a disease as required by the election requirement. In a telephone conversation with Amy DeCloux on 7/18/06 applicant further elected the disease "heart failure" with traverse. Applicant is reminded that the claims which do not recited a specific disease are considered "linking claims" with respect to the restriction to a single disease, and should the generic linking claims become allowable, the restriction among different diseases will be withdrawn in accordance with linking claim practice.

Priority

2. In claim 7, the limitation "detecting...in an unfractionated sample of whole blood" and in claim 8, the limitation "from RNA extracted from an unfractionated sample of whole blood" have basis the instant application when a combination of teachings are considered including at least examples 10-25 which teach that "total RNA was extracted from a drop of peripheral whole blood (see, for example, p. 47, line 15)" and page 11, line 26 which teaches applying probes or primers "directly" to a drop of blood. However, these limitations do not appear to have basis in the parent application which does not have statement or exemplification of total RNA extraction from a drop of whole blood. Therefore, the priority date for these claims is the instant filing

date, 6/20/03. A similar amendment was set forth in parent application 10/268730, and applicant points to support in that specification (see remarks dated 4/25/05 in parent application 10/268730, at page 5). However, upon careful examination, the examiner was unable to locate basis for these limitations in the parent application. A complete analysis follows.

First, applicant points to page 1, paragraph 13 and 14 of the parent application and page 3 paragraphs 36-38 (the page and ¶ numbers refer to the pre-grant publication US 2004/0014059). Paragraph 13 of the parent is identical to the paragraph in the instant application on page 6 beginning at line 10, and most of the text of paragraph 14 is in the instant application in the paragraph beginning on page 6, line18. The paragraphs on page 3 are also very similar to the paragraph on page 6 of the instant application. These paragraphs discuss the analysis of "whole blood samples" but provide no support regarding how the sample will be treated with regard to fractionating the sample or not fractionating the sample, extraction or not extraction, etc.

Applicant points to p. 4, ¶42, which is identical to the paragraph on page 33, beginning at line 10 of the instant application. This paragraph states "RNA was extracted from human tissues," giving a list that includes whole blood, but is again silent as to how the RNA was extracted.

Applicant points to Figure 5 and the corresponding description of Figure 5. These are the same in the parent application and in this application with the description of figure 5 appearing on page 8 of the instant application. Figure 5 shows levels of insulin and ZFP expressed in a drop of blood, and then further shows levels of insulin gene in "each fractionated cell from whole blood," with figure 5C giving levels for cell types labeled G.R., CD 3+, CD 19, and MONO. Clearly in figure 5C different blood cell types were fractionated from one another.

However, the methods which resulted in the data given in Figure 5A and 5B are discussed in example 6 (beginning on page 35) and state that "a drop of blood was extracted to obtain RNA" but is silent as to the extraction procedure, that is whether or not extraction included a fractionation step in which the cellular matter in blood was separated from plasma, for example. In discussing basis in the specification for this limitation, applicant stated that this limitation refers to "a sample of whole blood which has not been fractionated into cell populations and includes a drop of blood (see remarks dated 4/25/05 in parent application 10/268730, at page 5)." While this definition is clearly within the scope of "unfractionated" it is not an exclusive definition of "unfractionated," which, on it's face also requires that the blood sample itself was never fractionated into constituent parts such as plasma versus cells. The parent application further provides a statement that probes and primers may be "applied directly to a drop of blood (see parent ¶0079)." Such application would appear to expressly exclude the RNA extraction set forth in claim 8. Regarding claim 7, this does not provide basis for an "unfractionated sample of whole blood" because, while applying primers directly to a blood sample may exclude fractionating the sample, it does not only exclude fractionating the blood cells or the constituents of the blood, it also excludes, for example, extraction of the RNA from the sample. While the specification provides clear basis for methods wherein cell types within blood are not fractionated (¶0078 of the '268730 parent), and the specification provides clear basis for methods wherein a centrifuged pellet, which would clearly contain cellular matter is treated for use in RT-PCR, and the specification of the parent application provides basis for methods wherein primers or probes are provided "directly" to whole blood, the specification does not appear to provide basis for methods where unfractionated whole blood is extracted (as expressly set forth in instant

claim 8) or wherein detection occurs in "unfractionated sample of whole blood" since this embodiment is inclusive of both the genus where RNA from whole blood is extracted or not extracted, as set forth in instant claim 7.

This conclusion applies to the instant claims when "unfractionated sample of whole blood" is interpreted to mean that prior to RNA extraction or prior to amplification or detection the blood sample is not separated into constituent parts, at least excluding the separation of cells from the plasma of the whole blood sample, and as a result the total blood sample is subjected to the extraction method. The scope and meaning of this limitation are discussed in more detail in a 112 2nd rejection in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 9 includes a new limitation which appears to be new matter, namely the recitation that "the subjects having said disease are asymptomatic with respect to said disease." This generic claim encompasses the selection of markers in any possible disease. The remarks filed with the amendments to the claims do not identify basis for amended claim 9. The specification

provides a single example where differential expression of insulin between control patients, diabetic patients, and a person having asymptomatic diabetes is detected (Example 6, see top of page 36). However, the specification does not provide any discussion of how the disclosed methods could be applied to any patient asymptomatic for any disease. For example, there is no discussion of patients who are "asymptomatic" for heart failure being used to identify markers useful for diagnosing heart failure, or even how such analysis would be carried out. The specification does not generally describe or discuss the use of asymptomatic patients for marker identification for any or all diseases, as encompassed by the instant claim, and so this claim is rejected for new matter because the breadth of the claim does not appear to be contemplated in the instant specification.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 7-10, 13, 16-17 and 19-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejected claims are indefinite over the recitation of "an unfractionated sample of whole blood" which is recited in claim 7 and "from RNA extracted from an unfractionated sample of whole blood" in claim 8. The remaining claims depend from either claim 7 or claim 8 and are indefinite over these recitations as well. The specification does not define what is meant by an "unfractionated sample of whole blood." On its face, such a limitation appears to mean that the whole blood sample is not separated into constituent parts, however, interpretation of the

claim in light of the specification, pending claims, and prosecution history of the parent application (10/268730) results in ambiguity with regard to the meaning of this claim limitation.

For example, it is not clear if this limitation means that the detection occurs "directly" on a blood sample (as set forth on page 11, line 26 of the specification) which implies that the blood sample is not separated into any parts, or if this limitation encompasses some separation of parts, for example as expressly set forth in claim 8 where RNA is extracted from an unfractionated whole blood sample. This recitation contradicts itself since the extraction of RNA from a whole blood sample is itself a process of fractionating the whole blood sample, thus to obtain the a constituent part of the sample separate from the rest of the sample, namely the RNA. Thus, the claims themselves seem to imply that some level of separation of parts of a whole blood sample is encompassed within the recitation of an "unfractionated whole blood sample," but the specification does not provide any guidance for what level of separation of parts is implied.

One might interpret detecting in "unfractionated sample of whole blood" as requiring that the detection occur relative to RNA that was extracted from the entire blood sample without any prior separation of parts, which could be accomplished by direct extraction of the whole blood without separating removing the plasma from the blood sample, for example.

Applicant set forth still a different definition for this claim limitation in the parent application. In discussing basis in the specification for this limitation, applicant stated that this limitation refers to "a sample of whole blood which has not been fractionated into cell populations and includes a drop of blood (see remarks dated 4/25/05 in parent application 10/268730, at page 5)." This definition for unfractionated sample of whole blood set forth by

applicant would, therefore, allow a fractionation of the cellular material prior to RNA extraction (as exemplified in the instant specification in Example 5).

And so it is unclear what the metes and bounds of the phrase "unfractionated sample of whole blood" actually encompasses in light of the lack of definition of the phrase in the specification and the many, conflicting possible interpretations in light of the specification, pending claims, and remarks by applicant.

The claims are also indefinite over the recitation "said gene being detectable in said sample" in both claims 7 and 8. This phrase is indefinite because whether or not something is "detectable" is a latent property and could be dependent upon methodology used, as opposed to whether or not the gene itself is actually being expressed in the sample. Thus, it is not clear if applicant intends to recite that the gene is expressed in the control sample (or samples) or if it simply must be able to be detected if it were being expressed. Further, it is not clear if this limitation means that the gene is actually detected in the control sample or if a quantification of zero expression in the control sample would be encompassed within the claims.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Ditkoff et al. (Surgery, December 1996, Vol. 120, pages 959-965).

With regard to claim 1, Ditkoff et al. teach a method for diagnosing or prognosing a disease in an individual comprising determining the level of expression of a gene in a blood sample and detecting a difference of said level of expression of said gene in said blood sample relative to the level of expression of the same gene of a control, wherein a difference in expression levels is indicative or predictive of said disease. Namely, Ditkoff *et al.* complete amplification of RNA isolated from whole blood samples using RT-PCR (p. 960-961) using primers specific for a gene expressed in thyroid tissue (Fig. 1A), more specifically primers specific to the thyroglobulin gene transcripts. Ditkoff et al. complete their detection on an unfractionated whole blood sample (p. 960). The method used by Ditkoff detects RNA via the detection of a cDNA that is an EST. Ditkoff *et al.* teach a method for detecting expression of a gene in blood from a subject, comprising the step of detecting in cDNA from a blood sample the presence of an a cDNA complementary to a gene expressed in a non-blood tissue, wherein detection of said cDNA is indicative of expression of said gene in said blood sample.

Ditkoff et al. teach a method which additionally comprises a step of comparing the amount of said cDNA in said sample with the amount in a blood sample control, wherein detection of a difference in the amount of said cDNA compared with said blood sample control indicates a difference in the expression of said gene encoding said cDNA in said sample. Namely, Ditkoff *et al.* teach the amplification of both healthy subjects and test subjects and the comparison of the two expression profiles for the purpose of diagnosing metastatic cancer (p. 959-960, Table, p. 963).

Regarding claims 2 and 4, Ditkoff et al. teach comparison of the blood sample gene expression to the level of expression in a thyroid tissue sample, and the "same" level of expression, that is expression in fact, is indicative of disease. For this claim the recitation "same level of expression" is met by Ditkoff et al. since they make a yes or no observation, and the expression detected in the diseased sample is "the same" as in the thyroid tissue. Furthermore, Ditkoff et al. teach the comparison of the amplification among each of the patients, teaching that all patients with metastatic disease had an amplification product for the test, and thus, each of these patients may be considered a "diseased control" relative to the other patients.

Regarding claim 3, Ditkoff et al. specifically show comparison of diseased patients to non-cancerous controls.

Regarding claim 5, Ditkoff et al. teach testing the blood of more than one individual, and regarding claim 6, the individuals are undergoing treatment for thyroid disease (p. 961 and throughout).

Thus, the teachings of Ditkoff et al. meet the limitations of the rejected claims.

8. Claims 1-10, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26, 27, 32, 33, 34, 35, 36, and 37 are rejected under 35 U.S.C. 102(a) and 102(b) as being anticipated by Sharma et al. (WO 98/49342, as cited in IDS).

As discussed previously in this office action, the instantly filed claims are not supported by the previously filed applications. Thus, this reference, published 5 November 1998 is available as prior art under 102(b). Even in the event that applicant is able to show basis for the

instantly pending claims to the provisional application filed 1/6/99, or to any previously filed application, this reference will still be available under 102(a). Both rejections are applied in this office action in the interest of compact prosecution.

Regarding claim 7, Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely, Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of mRNA from unfractionated whole blood samples, where unfractionated is interpreted as meaning that the cell types within blood were not separated from one another (p. 35, section 5.1.1). Sharma et al. teach quantifying the level of expression and determining a difference between the quantified level in the sample from the diseased subject and a similarly quantified level of genes of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Regarding claim 8, Sharma et al. teach that these methods are carried out by producing amplification products from RNA extracted from an unfractionated sample of whole blood (p. 18 and p. 35, Example 5).

Regarding the requirement that the subject genes are genes that are expressed in blood and non-blood tissue of a subject not having said disease, this is considered to be an inherent property of at least some of the genes that would be detected by the methods taught by Sharma et

al. Sharma et al. appear to be using substantially the same method steps as used by applicant, and so the detected transcripts would be expected to include genes expressed in blood and non-blood tissue of a subject not having said disease.

Regarding claim 9, Sharma et al. teach that the invention can detect diseases years before other subjective or objective symptoms may appear (p. 11, third full ¶).

Regarding claim 10, Sharma et al. teach that diagnostic patterns can be provided that include markers of disease progression (p. 7, first ¶).

Regarding claims 16, 36, and 37, the sample taught by Sharma et al. is blood. Neither the specificaiton nor the claims provide a definition of how much blood is in a "drop," and so, any size blood sample is considered a drop, including the blood samples taught by Sharma et al.

Regarding claims 17 and 19, Sharma et al. teach the detection of many genes, including second, third, etc. (p. 16) genes and teach the sampling of more than one diseased and/or control subject to determine quantified levels of expressed markers (p. 21, first full ¶).

Regarding claims 20, 21, 24 , Sharma et al. teach detecting RNA by detecting cDNA derived from RNA (p. 18, steps (c) and (d), for example).

Regarding claim 22, Sharma et al. teach the use of primers that are specific for said gene and for any gene, relative non-coding sequences in the sample, as they teach using primers taken from the polyA tail and cap of the RNA (p. 12, 3rd full ¶), and these are specific to genes.

Regarding claims 23, 25, 26, Sharma et al. teach quantifying the level of control RNA in said sample (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach isolating the control RNA into bands on an electrophoresis gel for quantification (p. 13).

Regarding claim 27, Sharma et al. teach isolating RNA via extraction prior to the detection step (p. 12).

Regarding claims 32 and 33, Sharma et al. teach that the subjects are human (p. 7, 2nd full ¶).

Regarding claims 34 and 35, Sharma et al. teach that control subjects should be free of disease (p. 9, first full ¶).

Regarding claims 1-6, Sharma et al. teach that the probe sets identified by their methods can be used in a method of diagnosing or identifying disease which comprises assessing the amount of mRNA or cDNA hybridizing to test probes and comparing this to a control (a "standard diagnostic pattern") to determine the degree of correlation indicative of the presence of said disease or condition or a stage thereof in the organism under investigation (p. 22 and following). Sharma et al. teach using normal and diseased samples as controls (p. 22 final ¶). Sharma et al. teach comparison to a profile from a diseased patient and that if the profiles coincide the an aliment and its stage can be diagnosed with great certainty (p. 24, final ¶, for example). Sharma et al. teach that samples may be taken from one or more individuals to create the control panels (p. 22-23). Sharma et al. teach applying these methods to make patterns for tracking treatment to disease (p. 11, 2nd full ¶).

Thus, the teachings of Sharma et al. anticipate the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 7, 8, 16, 20-32, 34, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagai et al. in view of Kephart (Promega Notes Magazine, Number 62, p. 11-15, 1997).

Regarding claim 7, Nagai et al. teach a method comprising the steps of detecting the presence of RNA encoded by a gene expressed in blood and in non-blood tissue of a subject not having said disease in a sample of whole blood from each of one or more subjects having said disease, and quantifying a level of said RNA in said sample and determining a difference between said level and a quantified level of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects, said control RNA being encoded by said gene and being detectable in said sample from said control subjects, said difference identifying said gene as a marker of said disease. Namely, Nagai et al. teach the detection of the D3 dopamine recteptor in the peripheral blood of patients with Parkinson's disease and in the blood of healthy controls (p. 791), and teach that patients with disease have lower expression of the receptor than controls, and that this difference is significant between the two populations (p. 792-793). Nagai et al. complete their analysis using RT-PCR, and thus produce amplificaiton products from the sujbects, as required in claim 8.

Regarding claims 16 and 36, the sample taught by Nagai et al. is blood. Neither the specificaiton nor the claims provide a definition of how much blood is in a "drop," and so, any size blood sample is considered a drop, including the blood samples used by Nagai et al.

Regarding claims 20, 21, 22, the expression is generated by detecting and cDNA/EST producted with gene specific primers via RT-PCR on extracted RNA.

Regarding claims 23, 28, 29, 30, 31, the expression of test and control D3 receptor is compared to the housekeeping gene beta-actin (p. 791-793).

Regarding claims 24, 25, 26, Nagai et al. quantify the level of amplificaiton product from the control subjects, and Nagai et al. run the amplificaiton products onto a gel, which isolates the control RNA (p. 792).

With regard to claim 27, Nagai et al. extract total RNA, and thus first isolate RNA prior to detection.

Regarding claim 32 , the subjects are human.

Regarding claims 34, the control subject does not have Parkinson's disease.

The teachings of Nagai et al. do not teach detection of gene expression in unfractionated samples of whole blood, where the limitation "unfractionated" requires that the whole blood sample is not separated into constituent parts prior to RNA extraction methodology.

Kephart teaches a method for rapid isolation of RNA from small quantities of human whole blood for RT-PCR analysis. Kephart teaches "techniques routniely used to purify RNA from blood require relatively large quantities of starting material to isolate peripheral blood cells prior to extraction," and instead provide methods to isolate RNA from whole blood (p. 11).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Nagai et al. so as to have avoided the step of isolating lymphocytes using a method as taught by Kephart. One would have been motivated to modify the methods taught by Nagai et al. as taught by Kephart in order to avoid

the need to isolate the blood cells, and to utilize the systems taught by Kephart since Kephart teaches that they "enable quick and simple RNA preparation that can be completed in 20-120 minutes, and are appropriate for high-throughput analysis of both RNA and DNA species present in small numbers of white blood cells, serum or whole blood samples (p. 14)." Thus, at the time the invention was made, the claimed invention was prima facie obvious.

11. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. in view of Port et al. (US 5733728).

Instant claim 13 depends from claim 7 or claim 8. Regarding claim 7, Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely, Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of mRNA from unfractionated whole blood samples, where unfractionated is interpreted as meaning that the cell types within blood were not separated from one another (p. 35, section 5.1.1). Sharma et al. teach quantifying the level of expression and determining a difference between the quantified level in the sample from the diseased subject and a similarly quantified level of genes of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Regarding claim 8, Sharma et al. teach that these methods are carried out by

producing amplification products from RNA extracted from an unfractionated sample of whole blood (p. 18 and p. 35, Example 5).

Regarding the requirement that the subject genes are genes that are expressed in blood and non-blood tissue of a subject not having said disease, this is considered to be an inherent property of at least some of the genes that would be detected by the methods taught by Sharma et al. Sharma et al. appear to be using substantially the same method steps as used by applicant, and so the detected transcripts would be expected to include genes expressed in blood and non-blood tissue of a subject not having said disease.

Shama et al. teach the application of their method broadly to a variety of diseases, but does not specifically teach using their methods to identify markers for heart failure. However, at the time the invention was made, heart failure was a known human condition, and the differential expression of genes in blood tissue as a marker of heart failure had previously been disclosed at least by Port et al. (see Col. 2-3). It thus, would have been prima facie obvious to one of ordinary skill in the art to have modified the methods taught by Sharma et al. so as to have applied them to the disease of heart failure. One would have been motivated to apply to apply the methods taught by Sharma et al. to heart failure in order to identify markers that are expressed in blood that can be used to profile patients that might suffer from heart failure.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-10, 13, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 and 22 of copending Application No. 11/313302. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application either anticipate or make obvious on their face the claims of the instant application. The claims of the copending application provide methods for identifying biomarkers based on differential expression of RNA transcripts expressed in blood of patients having disease or not having disease compared to the other, as is claimed in the instant application. The claims of the copending application further provide methods for diagnosis and prognosis based upon such markers (see claim 17 therein). The claims of the copending application are silent as to particular sampling methodology and expression analysis methodology used, but the particular methods used in the instantly claimed invention were routinely used to detect gene expression in blood at the time the invention was made, and thus the claimed invention is prima facie obvious in view of the copending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-36 of copending Application No. 10/989191. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to methods of diagnosing or prognosing schizophrenia or bipolar using steps of determing the expression level of two or more RNA transcripts expressed in blood of individuals, referring specifically to particularly expressed biomarkers in claims 24, 25, and 36, and teaching the use of quantitative RT-PCR in claim 30. The claimed invention is silent as to the status of the blood sample ("unfractionated"), however, at the time the invention was made it was routine to obtain expression profiles from blood samples without separating cell types, and given the disclosure of the claims of the copending application, this embodiment would have been prima facie obvious. The claims of the copending application are silent as to particular sampling methodology and expression analysis methodology used, but the particular methods used in the instantly claimed invention were routinely used to detect gene expression in blood at the time the invention was made, and thus the claimed invention is prima facie obvious in view of the copending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-35 of copending

Application No. 10/980850. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to methods of diagnosing or prognosing liver cancer using steps of determing the expression level of two or more RNA transcripts expressed in blood of individuals, referring specifically to particularly expressed biomarkers in claims 17-20, and teaching the use of quantitative RT-PCR in claim 26. The claimed invention teaches using whole blood samples and samples from drops of blood (claims 22 and 23), and at the time the invention was made it was routine to obtain expression profiles from blood samples without separating cell types, and given the disclosure of the claims of the copending application, this embodiment would have been prima facie obvious. The claims of the copending application are silent as to particular sampling methodology and expression analysis methodology used, but the particular methods used in the instantly claimed invention were routinely used to detect gene expression in blood at the time the invention was made, and thus the claimed invention is prima facie obvious in view of the copending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 26-27, 30-33, and 36-62 of copending Application No. 10/268730. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or obvious in view of, the copending claims. For example, copending claim 26 teaches all of the limitations of instant claim 7, with copending claim 27 anticipating instant claim 8. The claims

of the copending application do not teach methods of diagnosis and prognosis as set forth in instant claims 1-6, but since the claims of the copending application specifically set forth that the differently expressed genes are "indicative of disease in said subject" it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods taught in the copending application to diagnose disease. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-10, 13, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-31 and 36 of copending Application No. 10/802875. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are directed towards an invention that is a species of the instantly generically claimed invention, namely the identification of genetic markers and the diagnosing or prognosing of coronary artery disease using methods as set forth in the instant claims. For example, claim 1 of the copending application teaches determining the level of one or more gene transcripts in blood obtained from individuals having coronary artery disease, comparing that to one or more individuals not having coronary artery disease, and identifying those genes that have differences as genetic markers for coronary artery disease. The claim does not specifically state that these are genes that are expressed in blood and non-blood tissue, as required by instant claim 7, for example, but this is an inherent property of many of the genes set forth in claim 8 of the copending application (which refers to genes set forth in Table 3L), and further this is provided by the method of claim

13, which depends from each of the independent claims of the copending application. Further, claims 10-12 of the copending application are directed towards methods of diagnosing or prognosing coronary artery disease using gene expression analysis. The copending claims teach using whole blood samples from one or more individuals (claim 14, for example), and teach using quantitative RT-PCR to complete the analysis (claim 19 of the copending application, for example). Regarding the further method limitations of the instant claims, such as claims 28-31, these would have been prima facie obvious over the claims of the copending application in view of the state of the prior art which teaches methods for completing quantitative PCR methods that include using controls and housekeeping genes to quantify gene expression products.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 47 of copending Application No. 10/809675. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are directed towards an invention that is a species of the instantly generically claimed invention, namely the identification of genetic markers and the diagnosing or prognosing of osteoarthritis using methods as set forth in the instant claims. For example, claim 1 of the copending application teaches determining the level of one or more gene transcripts in blood obtained from individuals having osteoarthritis, comparing that to one or more individuals not having osteoarthritis, and identifying those genes that have differences as genetic markers for osteoarthritis. The claim does not specifically state that these are genes that are expressed in

blood and non-blood tissue, as required by instant claim 7, for example, but this is an inherent property of many of the genes set forth in claim 8 of the copending application (which refers to genes set forth in Table 3O-3AB), and further this is provided by the method of claim 15, which depends from each of the independent claims of the copending application. Further, claims 9-13 of the copending application are directed towards methods of diagnosing or prognosing osteoarthritis using gene expression analysis. The copending claims teach using whole blood samples from one or more individuals (claim 16-17, for example), and teach using quantitative RT-PCR to complete the analysis (claim 21 of the copending application, for example). Regarding the further method limitations of the instant claims, such as claims 28-31, these would have been prima facie obvious over the claims of the copending application in view of the state of the prior art which teaches methods for completing quantitative PCR methods that include using controls and housekeeping genes to quantify gene expression products.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. The following statements of rejection are provided without further analysis because they are very similar to the analysis set forth for rejections over applications 10/802875 and 10/809646 in this office action. These additional applications have claimed inventions which differ from one another primarily with regard to disease under study and related genes:

20. Claims 1-10, 13, 16-17, and 19-37 are further provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812646.

21. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812702.

22. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812707.

23. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812716.

24. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812731.

25. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-40, 47 and 60 of copending Application No. 10/812737.

26. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812764.

27. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812777.

28. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812782.

29. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-37, 42 and 52 of copending Application No. 10/812797.

30. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30, 35 and 43 of copending Application No. 10/812827.

31. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/813097.

32. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/816357.

33. Claims 1-10, 16-17, and 19-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812716.

Conclusion

34. No claim is allowed.

35. Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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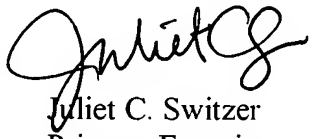
For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Juliet C. Switzer
Primary Examiner
Art Unit 1634

August 7, 2006